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Studies on 1-Azabicyclo Compounds. XXII.[1] Stereochemistry of 9a-Substituted Quinolizidine Methiodides[2]

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The stereochemistry of a number of the 9a-substituted quinolizidine methiodides was established, and confirmed from their ^{13}C-nuclear magnetic resonance (NMR) spectra. The N$^+$-methyl signals of the *trans* 9a-substituted quinolizidine methiodides were found to appear at lower field than those of the corresponding *cis* methiodides except for the 9a-cyano methiodides in their NMR spectra. On quaternization of the 9a-substituted quinolizidines with methyl iodide, the formation of the *cis* methiodide *vs.* the corresponding *trans* methiodide increased according to the order of the bulkiness of the 9a-substituents as $CH_2NO_2 > CH_2OH > CH_3 > CN > H$.

It is well known that substituted quinolizidines exist in a *trans*- and/or a *cis*-fused conformation and that those having an axial bulky substituent (R) in a *trans* conformation (Ia) exist predominantly in a *cis* conformation (Ib) with an equatorial substituent (R).[4] In addition, the formation of two possible methiodides[5] by reaction of benzoquinolizidines with methyl iodide and the stereochemistry of methylquinolizidine methiodides[6] have been reported so far. Arata, *et al.* have obtained 9a-cyano,[7] 9a-hydroxymethyl-,[8] and 9a-nitromethylquinolizidine[9] methiodides, whose configurations were remained unsettled.

As there exist four 1,3-diaxial interactions between the substituent (R) and the hydrogens in the *trans* conformation (IIa) of 9a-substituted quinolizidines, the bulkier the substituent (R) becomes, the more unstable the *trans* conformation (IIa) would become in comparison with the *cis* conformation (IIb), and therefore, the more the formation of the *cis* methiodide (IId) *vs.* the *trans* methiodide (IIc) would increase on quaternization with

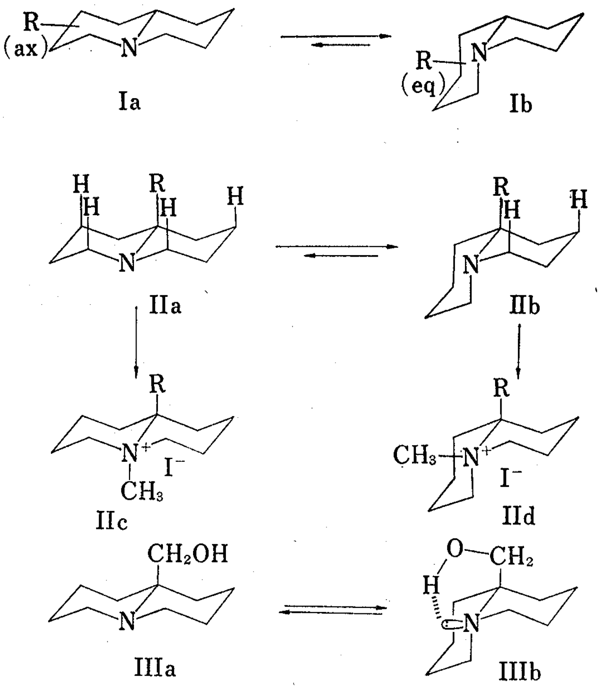

Chart 1

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[1] Part XXI: H. Kato, E. Koshinaka, Y. Arata and M. Hanaoka, *Yakugaku Zasshi*, **94**, 1566 (1974).

[2] Part of this work was reported at the 36th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, June 1973, Kanazawa.

[3] Location: *13-1, Takara-machi, Kanazawa, 920, Japan.*

[4] *cf.* F. Bohlmann, D. Schumann and C. Arndt, *Tetrahedron Letters*, **1965**, 2705.

[5] *cf.* J. Gadmer, *Arch. Pharm.*, **248**, 47 (1910).

[6] T.M. Moynehan, K. Schofield, R.A.Y. Jones and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637; C.D. Johnson, R.A.Y. Jones, A.R. Katritzky, C.R. Palmer, K. Schofield and R.J. Wells, *ibid.*, **1965**, 6797.

[7] Y. Arata, S. Yoshifuji and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969).

[8] Y. Arata and T. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 325 (1972).

[9] Y. Arata, T. Kikuti, M. Takahashi and T. Aoki, *Chem. Pharm. Bull.* (Tokyo), **22**, 1003 (1974).

methyl iodide. We now report the stereochemistry of a number of 9a-substituted quinolizidine methiodides and the influence of the 9a-substituents on the quaternization ratio of *trans* and *cis* methiodides.

The product obtained by quaternization of 9a-methylquinolizidine (IV)[10] with methyl iodide was fractionally recrystallized to give two isomeric methiodides in the 1:1 ratio: the methiodide (V), mp>300°, NMR τ: 6.83 (N^+-CH_3), less soluble in water, and the methiodide (VI), mp>300°, NMR τ: 6.97 (N^+-CH_3), comparatively soluble in water. The infrared (IR)

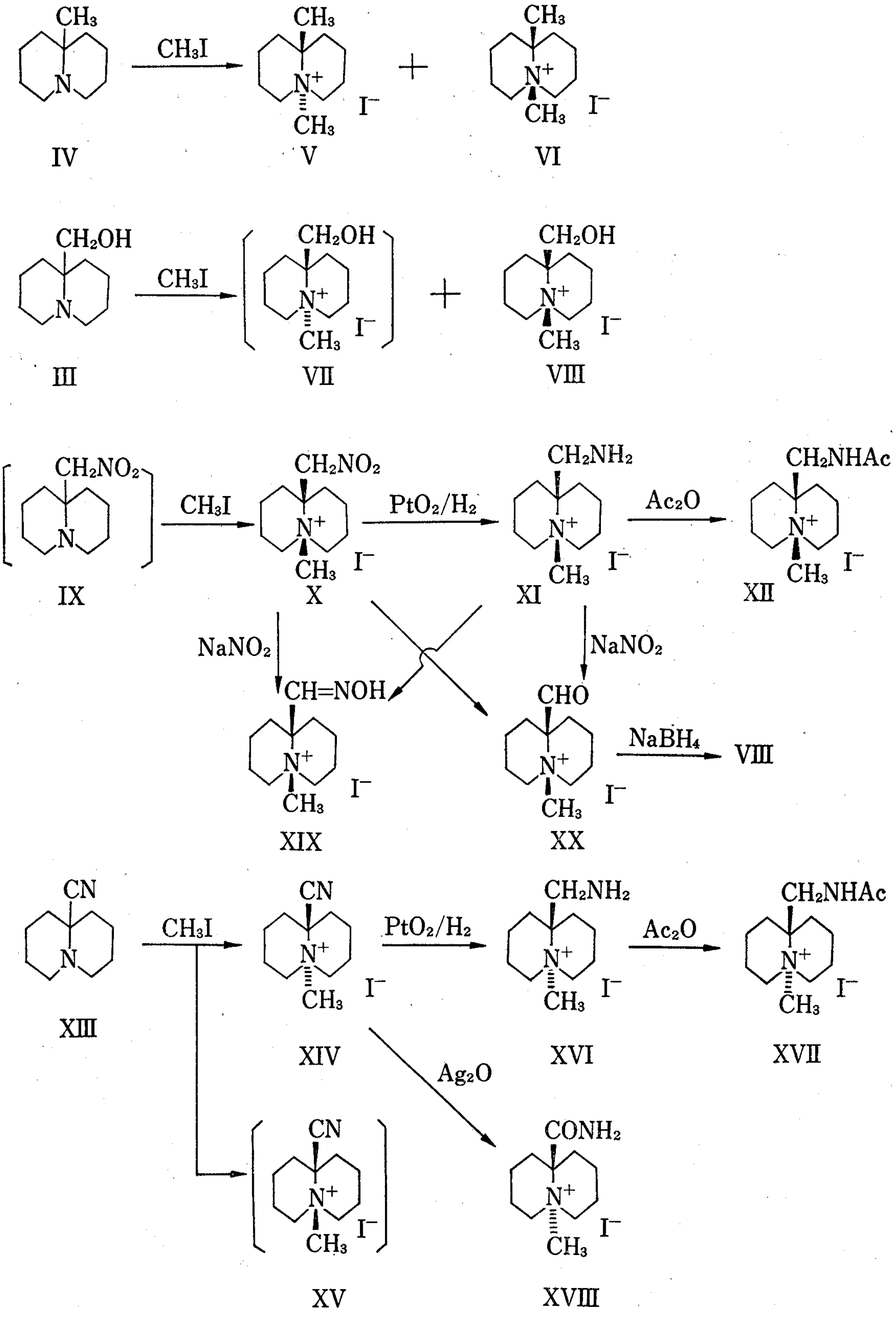

Chart 2

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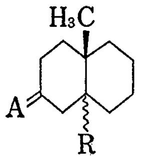
[10] N.J. Leonard, A.S. Hay, R.W. Fulmer and V.W. Gash, *J. Am. Chem. Soc.*, 77, 439 (1955).

and nuclear magnetic resonance (NMR) spectra of both methiodides were quite different from each other. Arata, *et al.* already reported[8] that 9a-hydroxymethylquinolizidine (III) exists as the conformational equilibrium mixture of IIIa and IIIb on the basis of its IR spectrum in carbon tetrachloride. The quaternization product of III, IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2750 (Bohlmann band), with methyl iodide exhibited N^+-methyl signals at 6.78 and 6.96 τ in its NMR spectrum. The measurement of the areas of both signals indicated that the product is a mixture of two isomeric methiodides (VII and VIII) in the 1:5 ratio. Recrystallization of the product from ethanol gave the major methiodide (VIII), mp>300°, NMR τ: 6.96 (N^+–CH_3) and the mixture of VII and VIII in the 1:1 ratio. The mixture could not be further separated into each other.

Based on the NMR spectral data in which angular methyl groups in *cis*-decalins show at lower field than those in *trans*-decalins,[11] Moynehan, *et al.*[6] have inferred the ring juncture for 1-, 2-, 3- and 4-methylquinolizidine methiodides. However, as shown in Table I, in *cis*- and *trans*-methyldecalins having another angular substituent, angular methyl signals in *cis*-fused series apper at higher field than those in *trans*-fused series except for the case with the cyano substituent in the NMR spectra. On the basis of these observations, *trans*-fused structure was postulated for V and VII, and *cis*-fused structure for VI and VIII. These assignments were proved to be correct from the ^{13}C-NMR spectra of V and VI. As the *trans*-fused structure (V) has a plane of symmetry included CH_3–C^{9a}–N^+–CH_3 in its molecule, C-1 and C-9; C-2 and C-8; C-3 and C-7; C-4 and C-6 would be expected to be magnetically equivalent to each other. Table II shows that the *trans* methiodide (V) exhibited four signals due to the ring carbons besides C-9a, and that the *cis* methiodide (VI) showed individual signals due to each of the ring carbons. The stereochemistry of V and VI was thus established as *trans* and *cis*, respectively. An attempt to transform VIII into VI was unsuccessfully carried out.

TABLE I. NMR Spectral Data of Angular Methyl Signals of Decalins (**1**) and Steroids (**2**, **3** and **4**)



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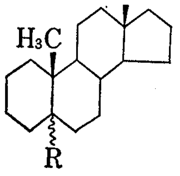

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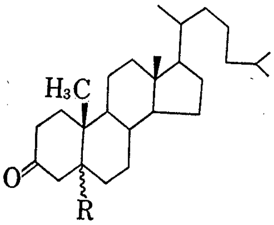

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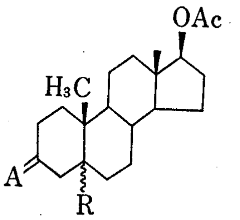

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	Compound		Chemical shift (τ)		Reference
	A	R	*trans*	*cis*	
1	H_2	OH	9.01	9.09	12
1	O	OH	8.78	8.87	12
2	—	OH	9.03	9.09	12
3	—	CH_3	8.74[a]	9.10[a]	13
4	O	CN	8.85	8.72	14, 15
4	OAc H	CN	9.04	8.82	14, 15

a) Other angular methyl signal at C_5 in **3** (*trans* and *cis*) appeared at 8.98 (C_5-α-CH_3) and 9.14 τ (C_5-β-CH_3), respectively.

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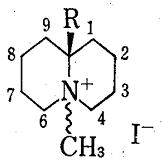
11) J.I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).
12) K.L. Williamson, L.R. Sloan, T. Howell and T.A. Spencer, *J. Org. Chem.*, **31**, 436 (1966).
13) W.G. Dauben and E.J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).
14) A.D. Cross and I.T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).
15) J.M. Jackman and G.Y. Sarkis, *Bull. Chem. Soc. Japan*, **42**, 1179 (1969).

Table II. ^{13}C-NMR Spectral Data of 9a-Substituted Quinolizidine Methiodides (V, VI, XVII, XII and XIV)



Compound			Chemical shift (ppm from TMS, in CF_3CO_2D)						
	R		C_1, C_9	C_2, C_8	C_3, C_7	C_4, C_6	C_{9a}	N^+-CH_3	Other signal
V	CH_3	(*trans*)	33.45	18.00	20.51	61.20	70.34	43.12	18.73 ($C-CH_3$)
VI	CH_3	(*cis*)	31.47 35.07	18.89 19.05	21.48	59.01 63.26	69.97	48.38	22.81 ($C-CH_3$)
XVII	CH_2NHAc	(*trans*)	28.39	18.06	20.14	61.40	72.22	44.80	22.72 ($CO\underline{C}H_3$) 38.54 (CH_2NH) 179.73 (CO)
XII	CH_2NHAc	(*cis*)	26.99 31.02	18.35 19.03	21.16	60.96 64.17	72.13	48.97	22.67 ($CO\underline{C}H_3$) 43.93 (CH_2NH) 179.88 (CO)
XIV	CN	(*trans*)	31.95	20.51	20.51	66.13	72.85	42.47	116.12 (CN)

Reaction of $\Delta^{1,9a}$-dehydroquinolizidine with nitromethane did not give the expected 9a-nitromethylquinolizidine (IX) presumably because of its instability, however, as previously reported, the same reaction was carried out in the presence of methyl iodide to give only one methiodide (X),[9] mp 224—225° (decomp.), NMR τ: 6.84 (N^+-CH_3), which was converted to the 9a-aminomethyl methiodide (XI),[9] NMR τ: 6.93 (N^+-CH_3), and then to the 9a-acetamidomethyl methiodide (XII),[9] NMR τ: 6.85 (N^+-CH_3). On the other hand, quaternization of 9a-cyanoquinolizidine (XIII),[16] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2760, 2670 (Bohlmann bands), with methyl iodide afforded a mixture of two isomeric methiodides (XIV and XV), NMR τ: 6.74 and 6.55 (N^+-CH_3), in the 17: 1 ratio calculated from its NMR spectrum, from which the major methiodide (XIV), mp 241—243° (decomp.), NMR τ: 6.74, was isolated by recrystallization from water. In order to correlate XIV to the above-mentioned methiodides (XI and XII), the methiodide (XIV) was hydrogenated over platinic oxide to give the isomeric 9a-aminomethyl methiodide (XVI), NMR τ: 6.68 (N^+-CH_3) though in a poor yield, which was then acetylated to the isomeric 9a-acetamidomethyl methiodide (XVII), NMR τ: 6.75 (N^+-CH_3). Treatment of XIV with silver oxide and then hydroiodic acid gave the amide (XVIII), NMR τ: 6.73 (N^+-CH_3). Chemical shifts of N$^+$-methyl signals of the methiodides (XVI and XVII) derived from XIV were lower than those of the isomeric methiodides (XI and XII) derived from X, respectively, suggesting that XIV, XVI, XVII and XVIII are *trans* and that X, XI, XII and XV are *cis*. These assignments were also confirmed unequivocally from the ^{13}C–NMR spectra of XIV, XII and XVII as shown in Table II. Contrary to the other 9a-substituted quinolizidine methiodides, the N$^+$-methyl signal of the *trans*- 9a-cyano methiodide (XIV) was found to appear at higher field than that of the corresponding *cis* methiodide (XV) presumably because of the anisotropy of the triple bond in their molecules. This observation is consistent with that in 5-cyano steroids.[14,15]

Reaction of XI with sodium nitrite in 50% aqueous acetic acid at room temperature, followed by treatment with sodium iodide, gave in 53% yield an unexpected product (XIX), mp 258—260° (decomp.), which was assumed to be 9a-hydroxyiminomethylquinolizidine methiodide from its elemental analysis and IR spectrum [ν_{max}^{KBr} cm^{-1}: 3375, 1620 (oxime)]. This reaction, when carried out at 80°, gave the formyl methiodide (XX), mp 246—248°

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[16] N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, 78, 1984 (1956).

(decomp.), IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1730, in 53% yield accompanied with a small amount of XIX. A mechanism for the reaction of XI with nitrous acid to XIX may be illustrated in Chart 3, since it was found that the bands with strong intensity appeared at 2255 ($N^+{\equiv}N$) and 1565 cm^{-1} (NO_2) in the IR spectrum of the product obtained in the beginning of the reaction and that the nitromethyl methiodide (X) was readily converted to XIX and XX under the same reaction condition as that for XI.

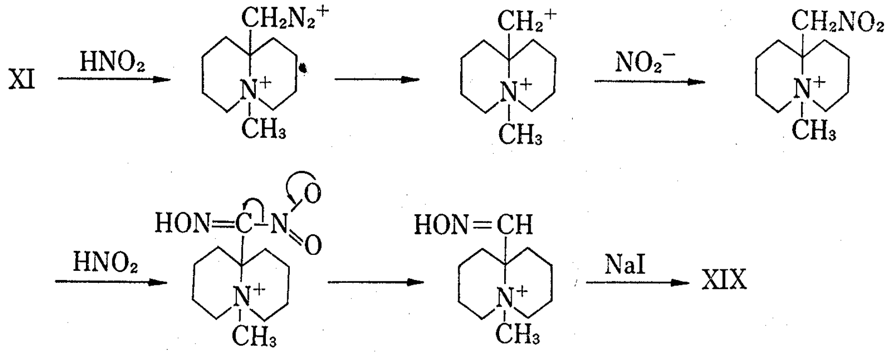
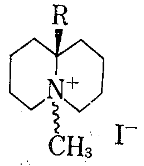


Chart 3

Reduction of the *cis* formyl methiodide (XX) with sodium borohydride afforded the *cis* hydroxymethyl methiodide, mp>300°, which was identical with the methiodide (VIII) derived from III in IR and NMR spectra. Therefore, the previously assigned stereochemistry of VII and VIII was proved to be correct as depicted.

TABLE III. NMR Spectral Data of N+-Methyl Signals of 9a-Substituted Quinolizidine Methiodides and The Quaternization Ratio of *trans* and *cis* Methiodides



Compound	Chemical shift (τ, in D_2O)		Ratio
R	*trans*	*cis*	*trans* : *cis*
H	7.04[6]	6.85[6]	1 : 0[6]
CN	6.74	6.55	17 : 1
CH_3	6.83[a]	6.97[a]	1 : 1
CH_2OH	6.78	6.96	1 : 5
CH_2NO_2		6.84	0 : 1
CH_2NH_2	6.68	6.93	
CH_2NHAc	6.75	6.85	

[a] The angular methyl signals at C-9a in *trans* and *cis* methiodides appeared at 8.35 and 8.51 τ, respectively.

Thus, the stereochemistry of 9a-substituted quinolizidine methiodides was clarified and these results are summarized in Table III and as follows:

1) The N+-methyl signals of *cis* 9a-substituted quinolizidine methiodides appeared at higher field than those of the corresponding *trans* methiodides except for the 9a-cyano methiodides in their NMR spectra.

2) On quaternization of 9a-substituted quinolizidines with methyl iodide, the formation of the *cis* methiodide in comparison with the *trans* methiodide increased according to the order

of the 9a-substituents as $CH_2NO_2 > CH_2OH > CH_3 > CN > H$.[17] This order corresponds essentially with that of their bulkiness.

3) The ^{13}C–NMR spectrum is the most conclusive method for the determination of the stereochemistry of 9a-substituted quinolizidine methiodides.

4) It is very interesting that the quaternization ratio (5: 1) of *cis* and *trans* methiodide obtained from 9a-hydroxymethylquinolizidine (III) was very similar to the equilibrium ratio (78: 22)[18] of *cis* and *trans* conformer (IIIb and IIIa) calculated from the IR spectrum of III.

Experimental[19]

***trans*- and *cis*-9a-Methylquinolizidine Methiodide (V and VI)**——A solution of 9a-methylquinolizidine[10] (IV, 600 mg) and MeI (2 g) in MeOH (1 ml) was kept standing in a refrigerator for 1 day and the reaction mixture was evaporated *in vacuo*. The residue was recrystallized from H_2O to give the *trans* methiodide (V, 426 mg (37%)), mp>300°, as colorless cubes. NMR τ: 6.83 (3H, s, N^+-CH_3), 8.35 (3H, s, $C-CH_3$). *Anal.* Calcd. for $C_{11}H_{22}NI$: C, 44.75; H, 7.51; N, 4.74. Found: C, 44.84; H, 7.51; N, 4.70.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized from H_2O to give the *cis*-methiodide (VI, 405 mg (35%)), mp>300°, as colorless pillars. NMR τ: 6.97 (3H, s, N^+-CH_3), 8.51 (3H, s, $C-CH_3$). *Anal.* Calcd. for $C_{11}H_{22}NI$: C, 44.75; H, 7.51; N, 4.74. Found: C, 45.06; H, 7.50; N, 5.00.

***trans*- and *cis*-9a-Hydroxymethylquinolizidine Methiodide (VII and VIII)**——1) From III: A solution of 9a-hydroxymethylquinolizidine[8] (III, 415 mg) and MeI (1 g) in MeOH (4 ml) was kept standing at room temperature for 3 days and the reaction mixture was evaporated *in vacuo*. The residue, NMR τ: 6.78 (0.5 H, s, N^+-CH_3), 6.96 (2.5H, s, N^+-CH_3), was recrystallized from EtOH to give the *cis* methiodide (VIII, 470 mg (62%)), mp>300°, as colorless scales. IR ν_{max}^{KBr} cm^{-1}: 3340 (OH). NMR τ: 6.01 (2H, s, $C\underline{H}_2OH$), 6.96 (3H, s, N^+-CH_3), (in d_6-DMSO) 4.75 (1H, br, OH, disappeared by addition of D_2O), 6.17 (2H, s, $C\underline{H}_2OH$), 6.92 (3H, s, N^+-CH_3). *Anal.* Calcd. for $C_{11}H_{22}ONI$: C, 42.45; H, 7.13; N, 4.50. Found: C, 42.70; H, 7.32; N, 4.27.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized from EtOH to give a mixture of the *trans* and *cis* methiodides (VII and VIII, 240 mg (31%)) in the 1: 1 ratio, as colorless fine crystals. NMR τ: 5.68 (1H, s, $C\underline{H}_2OH$), 6.01 (1H, s, $C\underline{H}_2OH$), 6.78 (1.5H, s, N^+-CH_3), 6.96 (1.5H, s, N^+-CH_3).

2) From XX: To a solution of XX (70 mg) in MeOH (5 ml) was added $NaBH_4$ (13 mg) at room temperature. The reaction mixture was stirred for 4 hr and evaporated *in vacuo*. The residue was recrystallized from EtOH to give VIII (53 mg (75%)), mp>300°, as colorless scales, which was identical with VIII obtained in 1) in IR and NMR spectra.

***trans*- and *cis*-9a-Cyanoquinolizidine Methiodide (XIV and XV)**——The crude methiodide[7] (1.10 g) obtained from 9a-cyanoquinolizidine[16] (XIII) was recrystallized from H_2O to give the *trans* methiodide (XIV, 730 mg), mp 241—243° (decomp.) (lit.[7] mp 242—243° (decomp.)), as colorless pillars. NMR τ: 6.74 (3H, s, N^+-CH_3).

The mother liquor was evaporated *in vacuo* to give a mixture of the *trans* and *cis* methiodides (XIV and XV, 362 mg), in the 5: 1 ratio, as a pale brown solid. NMR τ: 6.74 (2.5H, s, N^+-CH_3), 6.55 (0.5H, s, N^+-CH_3).

***trans*-9a-Aminomethylquinolizidine Methiodide (XVI)**——The methiodide (XIV, 1.0 g) was hydrogenated in H_2O (200 ml) over PtO_2 (500 mg) in an atmospheric pressure and room temperature for 20 hr. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was extracted with EtOH and the extract was evaporated *in vacuo*. The pale brown residue was recrystallized from H_2O to give XVI (85 mg (8.4%)), mp 226—227°, as colorless scales. IR ν_{max}^{KBr} cm^{-1}: 3420, 3240 (NH_2). NMR τ: 6.30 (2H, s, $C\underline{H}_2NH_2$), 6.68 (3H, s, N^+-CH_3). *Anal.* Calcd. for $C_{11}H_{23}N_2I$: C, 42.58; H, 7.47; N, 9.03. Found: C, 42.50; H, 7.19; N, 9.03.

***trans*-9a-Acetamidomethylquinolizidine Methiodide (XVII)**——A mixture of XVI (40 mg) and Ac_2O (5 ml) was heated at 100° for 1 hr with stirring and evaporated *in vacuo*. The residue was recrystallized from EtOH to give XVII (35 mg (76%)), mp 220—221°, as colorless pillars. IR ν_{max}^{KBr} cm^{-1}: 3280, 1680, 1530

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[17] Quinolizidine itself gave only *trans* quinolizidine methiodide on quaternization with methyl iodide.[6]

[18] Private communication from Dr. H.S. Aaron, Chemical Laboratory, Aberdeen Proving Ground, U.S.A., to whom we are very much obliged.

[19] All melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. IR spectra were measured with a Spectrophotometer IR-G, Japan Spectroscopic Co., NMR spectra with H-60-C, Japan Electron Lab. Co., using DSS as an internal standard in D_2O unless otherwise stated, and ^{13}C-NMR spectra with PS-100/PFT-100, Japan Electron Lab. Co., at 25.1 MHz using TMS as an internal standard in CF_3CO_2D.

(CONH). NMR τ: 5.82 (2H, s, $C\underline{H}_2NH$), 6.75 (3H, s, N^+-CH_3), 8.00 (3H, s, $COCH_3$). *Anal.* Calcd. for $C_{13}H_{25}ON_2I$: C, 44.32; H, 7.15; N, 7.95. Found: C, 44.33; H, 7.12; N, 7.98.

***trans*-9a-Carbamoylquinolizidine Methiodide (XVIII)**——To a solution of XIV (2.9 g) in H_2O (5 ml) was added Ag_2O (7.5 g) and the reaction mixture was stirred at room temperature in a dark place for 8 hr and filtered. The filtrate was evaporated *in vacuo* and the residue was dissolved in H_2O (2 ml). The solution was neutralized with 10% HI and filtered. The filtrate was evaporated *in vacuo* and the residue was recrystallized from EtOH to give XVIII (1.9 g (62%)), mp 286—287° (decomp.), as colorless cubes. IR ν_{max}^{KBr} cm^{-1}: 3325—3180 (NH_2), 1690 (CO). NMR τ: 6.73 (3H, s, N^+-CH_3). *Anal.* Calcd. for $C_{11}H_{21}ON_2I$: C, 40.75; H, 6.53; N, 8.61. Found: C, 40.87; H, 6.61; N, 8.35.

***cis*-9a-Hydroxyiminomethylquinolizidine Methiodide (XIX)**——1) From XI: To a solution of XI (300 mg) in 50% aq. AcOH (10 ml) was added $NaNO_2$ (150 mg) in small portions. The reaction mixture was kept standing at room temperature for 30 min and then evaporated *in vacuo*. The residue was dissolved in a small amount of H_2O and the solution was washed with $CHCl_3$ to remove I_2 deposited. To the aqueous layer was added NaI (200 mg). The precipitate was collected by filtration and recrystallized from H_2O to give XIX (165 mg (53%)), mp 258—260° (decomp.), as colorless cubes. IR ν_{max}^{KBr} cm^{-1}: 3375, 1620 (=NOH). NMR τ: 6.86 (3H, s, N^+-CH_3). *Anal.* Calcd. for $C_{11}H_{21}ON_2I$: C, 40.75; H, 6.53; N, 8.61. Found: C, 40.80; H, 6.59; N, 8.35.

2) From X: To a solution of X (405 mg) in 50% aq. AcOH (10 ml) was added $NaNO_2$ (200 mg) in small portions. The reaction mixture was treated in the same procedure as that described in 1) to give XIX (195 mg (51%)), mp 258—260° (decomp.), which was identical with XIX obtained in 1) in IR and NMR spectra.

***cis*-9a-Formylquinolizidine Methiodide (XX)**——1) From XI: To a solution of XI (300 mg) in 50% aq. AcOH (10 ml) was added $NaNO_2$ (150 mg) in small portions. The reaction mixture was heated at 80° for 1 hr and treated in the same procedure as that described for XIX to give the precipitate, which showed bands due to XX accompanied with faint bands due to XIX. The crude product was recrystallized from EtOH to give XX (158 mg (53%)), mp 246—248° (decomp.), as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1730 (CO). NMR τ: 6.70 (3H, s, N^+-CH_3). *Anal.* Calcd. for $C_{11}H_{20}ONI$: C, 42.72; H, 6.52; N, 4.53. Found: C, 43.00; H, 6.92; N, 4.98.

2) From X: To a solution of X (208 mg) in 50% aq. AcOH (5 ml) was added $NaNO_2$ (100 mg) in small portions. The reaction mixture was treated in the same procedure as that described in 1) to give XX (65 mg (22%)), mp 246—248° (decomp.), which was identical with XX obtained in 1) in IR spectrum.

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